REMARKS

Prior to this amendment, claims 1-43 were pending. Claims 3, 7-11 and 43 were rejected. Claims 4-6 and 12-16 were objected to, but, according to the Office Action, would be allowable if written in independent form. Claims 1-2 and 17-42 were withdrawn from consideration. Claim 3 has been amended. New claim 44 has been added. No claims have been cancelled. Accordingly, upon entry of this amendment, claims 1-44 shall be pending.

No new matter has been added by this amendment.

Applicants thank and acknowledge the Examiner's indication that claims 4-6 would be allowable if written in independent form. Because claims 12-16 depend from claims 4-6, claims 12-16 would also appear to be allowable with the parent claims in independent form. Applicants note, however, that claims 4-6 have not been written in independent form by this amendment because, for reasons that follow, it is believed that the amendment to claim 3 overcomes the present rejections, thereby rendering the rewriting of dependent claims 4-6 in independent form unnecessary.

Claim 3 has been amended to require that the step of enriching the cells for GGTA1 null cells be done without drug selection. Support for this amendment can be found in the specification and the originally-filed claims. For example, support for the amendment can be found at paragraphs 68 and 69 of the corresponding published application, US 2006/0242722 A1, as well as in Examples 1-4.

Claim 44 has been added, the support for which can be found in the specification and the originally-filed claims. For example, support for step (a) of claim 44 can be found in parallel to the support for claim 3. Support for steps (b) and (c) of claim 44 can be found paragraphs 17 and 54, as well as in Example 1-5.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

The rejections under 35 U.S.C. § 103 are overcome

The Examiner has rejected claims 3, 7-11 and 43 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,153,428 to Gustafsson et al. ("GUSTAFSSON") in view of Costa et al., "Expression of the Human 1,2-Fucosyltransferase in Transgenic Pigs Modified the Cell Surface Carbohydrate Phenotype and Confers Resistance to Human Serum-Mediated Cytolysis," FASEB J., 13:1762-1773 (1999) ("COSTA").

More in particular, the Office Action states that GUSTAFSSON discloses a process "for the enrichment and selection of porcine ES cells homozygous for a disruption in the gene encoding α-1,3-galactosyltransferase comprising the double selection of cells in antibiotic selection media, and then culture of viable cells." It further states that COSTA discloses "the analysis and selection by flow cytometry of the α(1,3) Gal epitope using anti-Galα-1,3-Gal antibodies on pig cells." The Examiner concludes that it would have been obvious to one of

ordinary skill to modify the method of enriching and selecting the porcine ES cells of GUSTAFSSON with the selection method of COSTA. Applicants disagree with the rejection. Nevertheless, Applicants have amended the claims to advance prosecution. In view of the claims as presently amended, Applicants believe that a conclusion of obviousness cannot be made in view of the U.S. Supreme Court's and the USPTO's current interpretation of obviousness under 35 U.S.C. § 103.

The PTO has issued Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 ("Guidelines") in view of the Supreme Court's recent decision in KSR International Co. v. Teleflex Inc., 550 U.S. __, 82 USPQ2d 1385 (2007), The Guidelines were published in the Fed. Reg., Vol. 72, no. 195, October 10, 2007. As pointed out in the Guidelines, the Supreme Court in KSR reaffirmed the analytical framework for determining obviousness as set forth in Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), and also held that the Federal Circuit's application of its teaching-suggestion-motivation test was too formalistic.

Under Graham, obviousness is a question of law based on underlying factual inquiries that address (1) the scope and content of the prior art, (2) the differences between the claimed invention, and (3) resolving the level of ordinary skill in the pertinent art. Consideration must also be given to secondary factors, such as, for example, evidence of commercial success, long felt but unsolved needs, failure of others, and unexpected results. The Supreme Court stated in KSR that "While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls." The Guidelines go on to state that "Once the *Graham* factual inquiries are resolved, Office personnel must determine whether the claimed invention would have been obvious to one or ordinary skill in the art."

The Guidelines proceed then to articulate seven independent rationales on which to properly base a rejection under 35 U.S.C. § 103: (1) combining prior art elements according to known methods to yield **predictable results**, (2) substitution of one known element for another to obtain **predictable results**, (3) use of known technique to improve similar devices, methods or

products in the same way, i.e., to obtain **predictable results**, (4) applying a known technique to a known device, method or product ready for improvement to yield **predictable results**, (5) choosing from a finite number of identified, **predictable solutions**, with a reasonable expectation of success, i.e., obvious to try, (6) evidence of design incentives or other market forces sufficient to prompt skilled artisan to vary prior art in a **predictable manner** to result in claimed invention, and (7) evidence of some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine prior art to arrive at claimed invention, i.e., **predictable** modification. All of these tests have the requirement of **predictability**. That is lacking in the present case.

The invention as presently claimed in claim 3 is directed to a method of selecting GGTA1 null cells comprising the steps of: (a) obtaining a line of cells obtained from a GGTA1 heterozygous pig or fetus; (b) enriching the cells for GGTA1 null cells without drug selection; and (c) scanning the line for a viable GGTA1 null cell. Claim 3 reflects the discovery by the present inventors, as captured at paragraphs 68 and 69 of the published application, that GGTA1 null cells may be enriched from a cell line obtained from a GGTA1 heterozygous pig without using a drug selection process. Paragraphs 68 and 69 are shown below to emphasize the differences between GUSTAFFSON and the presently claimed invention. Applicants especially note that the disclosure at paragraph 68, in fact, particularly distinguishes over GUSTAFFSON:

> [0068] **Previous efforts** to isolate GGTA1 null cells beginning with GGTA1 heterozygous cells have utilized transfection with a gene targeting vector **combined with a drug selection system** that differs from that used to select the heterozygous cells. See Gustaffson et al U.S. Pat. No. 6,153,428. Development and application of a second drug selection system has not been successful to date.
>
> [0069] In contrast, the present invention involves selection of cells with mutations in the functional allele of heterozygous GGTA1 cells or somatic recombination leading to GGTA1 null cells **without using a second drug selector such as G418**. Repeated selection against cells expressing GGTA1 is performed by exposure to affinity purified primate antibodies against the α-1,3-gal epitope followed by lysis with complement. As an

> alternative or supplement treatment, depletion of cells expressing GGTA1 is performed by, with or without first treating the cells with anti-gal reagents, including but not limited to, gal epitope ligands or anti-galactose-α(1,3)-galactose antibodies, followed by using the appropriately coated magnetic micro-beads. The antibody/complement treatment and the depletion can be repeated multiple times in any order. Use of the above processes results in a population of cells sufficiently enriched in GGTA1 null cells for direct use in nuclear transfer. Alternatively, enriched cell populations may be cloned, with or without additional selection with antibody and complement or depletion as described above. Similar selection may be performed with other agents which specifically bind the α-1,3-gal epitope and lead to cell death or permit physical separation of binding and non-binding cell populations.

As is apparent from paragraphs 68 and 69, the present invention, unlike the method of GUSTAFFSON, does not require any drug selection process in order to select or identify a GGTA-1 null cell starting from the heterozygous cell population. As stated in the Office Action, GUSTAFFSON "teaches a method for the enrichment and selection of porcine ES cells homozygous for a disruption in the gene encoding α-1,3-galactosyltransferase comprising the **double selection of cells in antibiotic selection media**, and then culture of viable cells."

Turning to the reference itself, GUSTAFFSON teaches as much. For example, GUSTAFFSON states that "Gene targeting by homologous recombination in swine requires several components, including the following: (A) a mutant gene targeting construct including the **positive/negative drug-selectable marker genes**...(B) embryonic stem cell cultures; and (C) the experimental embryology to reconstitute an animal from the cultured cells." See column 12, lines 13-19. The reference then goes on to disclose the use of a first gene targeting construct containing a **selectable drug marker** (neo gene – resistance to G418 drug), which is used to select cells with an inactivated GGTA1 allele. See column 12, lines 20-56.

GUSTAFFSON then goes on to teach that "ES cell clones that have undergone targeted mutagenesis of one allele of the α(1,3) galactosyltransferase locus are subjected to a second round of in vitro mutagenesis or used for reconstituting an animal that contains the mutation. A

second round of an in vitro mutagenesis can be carried out using an analogous targeting construction with hygromycin phosphotransferase hyg as **positive selectable marker gene**." See column 12, lines 57-63.

Thus, as recognized by the Examiner and as evidenced in the disclosure of the cited reference, GUSTAFFSON does not teach or fairly suggest the presently claimed method, in particular, a method of selecting GGTA1 null cells comprising the steps of: (a) obtaining a line of cells obtained from a GGTA1 heterozygous pig or fetus; (b) enriching the cells for GGTA1 null cells without drug selection; and (c) scanning the line for a viable GGTA1 null cell.

The gap between the teachings of GUSTAFFSON and the present invention as now claimed would not have been obvious to one of ordinary skill in the art at the time of filing. And, none of the above rationales provides a fair basis by which to conclude that the presently claimed invention is obvious. There is no basis, except hindsight, to believe that it would have been obvious to modify the method of GUSTAFFSON to exclude the use of drug selection during the second round of mutagenesis to inactivate the second remaining functional allele of the starting-point heterozygous GGTA-1 cell line. Nothing in GUSTAFFSON would suggest that its modification to avoid drug selection to obtain a null cell homozygous for GGTA1 would have **predicatably** yielded a GGTA1 homozygous cell, or that such a cell could have been used to obtain a viable nuclear transfer transgenic swine, as was shown by the present inventors (e.g., see Exampe 5). Instead, GUSTAFFSON suggests or teaches away from the present invention by reinforcing the use of drug-selectable markers as the conventional process by which to carry out gene targeted mutagenesis in swine. See e.g., column 12, lines 13-18. GUSTAFFSON does not at any point teach or suggest not using drug selection to construct or select a homozygous GGTA1 cell line.

COSTA does not cure the deficiencies of GUSTAFFSON. COSTA reports a study aimed at addressing the problem of acute xenograft rejection due to the presence of the Galα1,3-Gal antigen expression by carbohydrate remodeling. In particular, COSTA teaches the generation of

multiple lines of transgenic pigs that express various levels of HT in different swine cells, tissues and organs in order to minimize the expression of the Galα1,3-Gal antigen, which then, in turn, decreases natural antibody reactivity and results in significantly reduced complement activation, which, in turn, is aimed at improving acceptability of xenograft implants. See page 1771, column 1. The Examiner cites to page 1764, col. 2, which teaches that flow cytometry analysis and immunofluorescence techniques used by the authors, which included the use of purified human anti-Galα1,3-Gal antibodies to detect the Galα1,3-Gal antigen on the surface of pig cells by flow cytometry. COSTA does not teach or suggest, either alone or in combination with any part of GUSTAFFSON, a method of selecting GGTA1 null cells comprising the steps of: (a) obtaining a line of cells obtained from a GGTA1 heterozygous pig or fetus; (b) enriching the cells for GGTA1 null cells without drug selection; and (c) scanning the line for a viable GGTA1 null cell.

Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the Section 103 rejections of claim 3, 7-11 and 43. Claim 3 is nonobvious for at least the reasons given above. Claims 7-11 and 43 ultimately depend from claim 3, and are thus nonobvious for at least the same reasons noted above for claim 3. Moreover, the Examiner is thanked for already indicating that claims 4-6 would be allowable if written in independent form (as well as would be claims 12-16, which depend therefrom). These claims have not been rewritten by this amendment in independent form as it is believed that base claim 3 is nonobvious for the reasons given above.

In addition, Applicants respectfully request a clearer articulation of the basis or rationale supporting the Section 103 rejection. The MPEP states that "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with

some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at __, 82 USPQ2d at 1396." Applicants respectfully note that the Office Action does not appear to provide such a clear articulation as to the basis or rationale supporting its obviousness rejection and respectfully requests that the Examiner more clearly articulate same.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

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Respectfully submitted,

By: _____

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